Structure
Previews

Class II Cytokine Common Receptors: Something Old, Something New

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In this issue of *Structure*, Yoon and colleagues provide models of a low affinity cytokine common receptor, IL-10R2, in a ternary complex with two class II cytokines and their corresponding ligand-specific receptors, revealing the nature of their promiscuous interactions.

Cytokines are a diverse group of secreted polypeptides that regulate immune cell proliferation, differentiation, and function. Critical to their activities are cell surface receptors, which they engage to induce signaling that alters transcriptional responses. Cytokines were initially classified according to their functions, though in more recent years, bioinformatic and structural methods have been increasingly used (Bazan, 1990; Walter, 2004; Wang et al., 2009). One theme that has emerged is that cyokines from the same class often signal through similar or the same receptors and share overlapping functions. One such example is the cystine-knotted neutrophic factors, including glial-derived neutrophic factor, neuturin, persephin, and artemin, all of which signal through receptor heterodimers consisting of a ligand-specific receptor and a common receptor, known as RET (Wang et al., 2006). Other examples include the helical class I and class II cytokines, which also signal through a ligand-specific and a common receptor; common receptors for class I cytokines include gp130, γ_c, and β_c, while those for class II include IL-10R2 and IL-20R2 (Pestka et al., 2004; Wang et al., 2009).

Structural studies have shown that the similarity among ligands and receptors within classes is striking. Class I cytokines, for example, share a common α helical fold and signal in most cases through receptors with extracellular domains comprised of tandem fibronectin type III modules, single-spanning transmembrane domains, and intracellular domains that interact with soluble kinases. Structural studies have further revealed that ligands of this class generally engage their ligand-specific and common receptors in a similar overall manner, accounting for their overlapping functions (Wang et al., 2009). On the other hand, substantial differences exist, both in the manner by which the receptor extracellular domains are arranged relative to the plane of the membrane and the repertoire of cytoplasmic effectors that are activated (Wang et al., 2009). It is these similarities and differences that underlie the overlapping, yet often nuanced, functions that cytokines play in regulating complex immune responses in vertebrates.

Class II cytokines and receptors, the focus of the paper by Yoon et al. (2010) highlighted in this issue of *Structure*, share many similarities with their class I counterparts, including helical ligand folds, tandem fibronectin type III modules in the extracellular domains of their receptors, and the usage of common receptors (Table 1). Class II cytokines, however, do not bind class I receptors and the functions of these two classes are generally distinct, with the class I cytokines functioning to regulate the expansion or differentiation of tissues, and those of class II to minimize immune system damage caused by insult or injury.

Clearly, the structural characterization of class II cytokines in complex with their ligand-specific and common receptors is essential for obtaining a detailed understanding of how class II cytokines induce their overlapping yet distinct activities. Several class II cytokines, including IL-22, IL-10, and IL-10's Epstein-Barr virus (ebv) and cytomegalovirus (cmv) orthologs have been characterized in complex with their ligand-specific receptors;

Table 1. Class II Cytokines, Receptors, Signaling, and Biological Activities

Cytokine	Ligand-specific receptor (R1)	Common receptor (R2)	Signal transducer	Biological activity
IL-10	IL-10R1	IL-10R2	Jak1, Tyk2, STAT1 and 3	Immune suppression, anti-inflammatory
cmvIL-10	IL-10R1	IL-10R2	Jak1, Tyk2, STAT1 and 3	Immune suppression, anti-inflammatory
ebvIL-10	IL-10R1	IL-10R2	Jak1, Tyk2, STAT1 and 3	Immune suppression, anti-inflammatory
IL-22	IL-22R1	IL-10R2	STAT3	Acute-phase response, innate immunity
IL-26	IL-20R1	IL-10R2	STAT1 and 3	Mucosal and cutaneous immunity
IL-28, IL-29	IL-28R1	IL-10R2	Jak1, STAT1, 2, 3, and 5	Antiviral immunity
IL-19, IL-20, IL-24	IL-20R1	IL-20R2	Jak1, STAT1 and 3	Skin development, epidermal functions, inflammation
IL-20, IL-24	IL-22R1	IL-20R2	Jak1, STAT1 and 3	Skin development, epidermal functions, inflammation

Adapted from Pestka et al. (2004).

yet, in spite of intensive efforts, no structure has been reported for either of the class II common receptors, IL-10R2 or IL-20R2, either as a binary complex (BC) with ligand, or as a ternary complex (TC) with ligand and R1. Evidently, this is a consequence of the rather weak intrinsic affinity of the recombinant soluble common receptors for ligand, or their corresponding BCs, as quantitative binding studies reveal binding affinities in the micromolar to millimolar range (Yoon et al., 2005).

Yoon et al. (2010) have begun to fill this important void in our knowledge of class II cytokines by employing an alternative approach that involves: (1) structural determination of soluble IL-10R2 (sIL-10R2) alone; (2) site-directed mutagenesis of sIL-10R2, coupled with quantitative determination of the binding affinities of mutant sIL-10R2's for IL-22:sIL-22R1, cmvIL-10:sIL-10R1, and IL-10:sIL-10R1 BCs; and (3) a data-driven docking procedure to construct models of the corresponding TCs. These efforts yielded a tightly clustered ensemble of TCs that satisfied all of the experimental data for the IL-22 and cmvIL-10 TCs, but not the IL-10. The extent of convergence correlated closely with relative binding affinities (IL-10 bound most weakly), indicating that the docking approach, while very powerful, has limitations in light of a limited number of restraints and limited affinity, as would be expected.

Yoon's results reveal some surprising insights, the first and perhaps most important of which is that the common receptor binds in a manner that is not significantly different relative to a common receptor by class I cytokines, such as gp130 and γ_c. Specifically, it is observed that the overall shape of the TCs is that of a "Y," where the ligand-specific receptor (R1) forms the left arm, the common receptor (R2) the right arm, and the cytokine sits in the "V" in between (Figure 1). In addition to a similar overall manner of common receptor binding relative to class I cytokines, it is also observed that in both class II TC structures, a tyrosine residue forms nearly the same interaction with a hydrophobic cluster on helix D of the cytokine as that formed by either a tyrosine or phenylalanine in the class I common receptors, gp130 and γc (Wang et al., 2009).

These findings, which underscore the shared ancestry for class I and II cytokines, simultaneously provide insights into the means by which the common receptor adapts to bind multiple class II cytokines, including IL-10 and its viral orthologs, IL-22, IL-26, IL-28, and IL-29 (Table 1). In short, this occurs through a molecular swap in which clefts that are unique to IL-10R2 alternately engage protruding features of the cytokines. In the IL-22 TC, the cleft formed between the L3 and L5 loops of IL-10R2 selectively engages a protruding tyrosine on helix A of the cytokine (Figure 1A), while in the cmvIL-10 TC, the cleft formed between the L2 and L3 loops of IL-10R2 selectively engages a protruding knob centered about a threonine residue on helix D of the cytokine (Figure 1B). Importantly, these results highlight that the cytokine common receptors interact with their cognate receptors not only through evolutionarily conserved structural features, but as well, through recent evolutionary adaptations unique to individual class members; thus, just as tradition cites when two people join together—something old, something new.

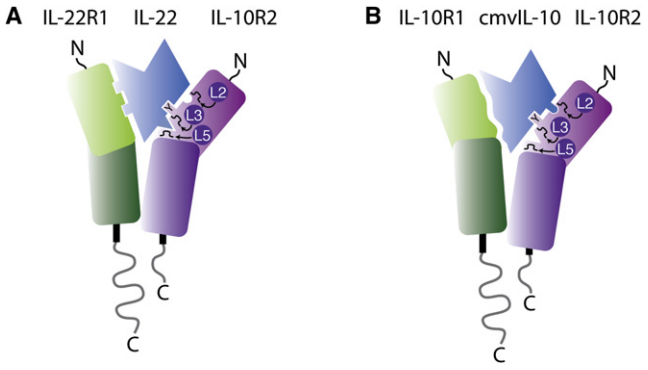

Figure 1. Mechanism of Promiscuous Cytokine Binding by the Class II Common Receptor, IL-10R2
Schematic diagrams depicting the tandem fibronection type III modules that comprise IL-10R2 (magenta) and the ligand-specific (green) in complex with two class II cytokines, IL-22 (A) and cmvIL-10 (B). Key structural determinants shared with class I cytokines ("Y"), yet promiscuity in binding class II cytokines (pockets formed by "L2-L3" and "L3-L5" loops and corresponding protrusions on the cytokines) are shown schematically.

One issue these new structures leave unanswered is the relative importance of the factors that enable recruitment of IL-10R2 into the signaling complex; based on the derived structures and mutants studied, it's likely that receptor-receptor contacts play a role, yet the membrane cannot be forgotten (Sebald and Mueller, 2003), as it likely plays an important role in increasing the effective concentration of the ligand and promoting receptor complex assembly. Another outstanding issue relates to how the structural organization of the receptor extracellular domains alters the structure of the intracellular domains and their interactions with the downstream signaling machinery. Answers to this question will not likely be achieved by a singular technique, but instead will require an integrated approach involving multiple methods, as done in the current study.

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